REMARKS

By the preliminary amendments presented, the specification has been amended to correct typographical errors at page 8, lines 13-28.

Also by the preliminary amendments presented, the Abstract has been rewritten to correct typographical errors and to more clearly recite that the present invention pertains to liquid compositions which have improved stability, and which are especially effective in the delivery of pharmaceutical actives.

Also by the preliminary amendments presented, Claims 4-7 and 9-20 have been canceled without prejudice. New Claims 22-36 have been added to incorporate the limitations of canceled Claims 4-7 and 9-20, and to recite claim dependency or reference to Claim 21.

Also by the preliminary amendments presented, Claim 21 has been amended to more specifically define the claimed oral composition as having the reducing agent solubilized in a phase different from the phase in which the pharmaceutical active is solubilized. Support for this amendment is found in the specification at page 8, lines 4-12.

Attached hereto is a marked-up version of the changes made to the specification, abstract, and claims as a result of the current amendments. The attached page is captioned **"Version with Markings to Show Changes Made"**.

Upon entry of the preliminary amendments presented, Claims 21 remains in this continuation prosecution application. Claims 22-36 are new in the present continuation prosecution application. No additional claims fee is due.

Invention Synopsis

The present invention is directed to stable liquid compositions which comprise a pharmaceutical active and a reducing agent, wherein the reducing agent provides for improved stability of these compositions especially when the compositions are formulated into various product forms such as liquid elixirs for treating symptoms associated with respiratory illnesses.

It has been found that a reducing agent can be included in liquid compositions containing a pharmaceutical active to enhance long term stability of the composition, provided that the reducing agent is solubilized in a solvent system separately from a solvent system used to solubilize the active. The solubilzation of the reducing agent in one solvent phase, and the active in another solvent phase, results in a stable, homogenous, liquid composition that is highly effective in the delivery of pharmaceutical active ingredients.

Formal Matters

Claim objection

Claim 5 of the parent application had been objected to for a typographical error in recitation of the term "terbuty" rather than the term "tert-butyl". Responsive to this objection, Claim 5 has been

canceled without prejudice, and new Claim 23 which incorporates the limitations of canceled Claim 5 now properly recites the term "tert-butyl", thus obviating this rejection as it would apply to the claims of the present continuation prosecution application which recite the term "tert-butyl".

Art Rejection

Claims 21, and 4-20 of the parent application had been rejected under 35 U.S.C. 102 as being anticipated by Gallo-Torres et al. (U.S. Patent 4,310,543). The Examiner contended that Gallo-Torres et al. disclose an oral composition as claimed by Applicants, wherein the composition comprises a pharmaceutical active, an active solvent such as polyethylene glycol, and a reducing agent such as bisulfite, thiourea or tert-butyl hydroquinone. Applicants submit that Claims 4-20 have been canceled without prejudice, thus obviating this rejection as it would apply to these claims. Applicants respectfully traverse this rejection as it would apply to Claims 21-36 of the present continuation prosecution application.

Gallo-Torres et al. disclose pharmaceutical compositions which are orally administered, and which comprise a prostaglandin pharmaceutical active and an ascorbic acid or ascorbyl palmitate stabilizer dissolved in a solvent such as polyethylene glycol. Gallo-Torres et al. further disclose that up to about 0.5% by weight of other stabilizes can be included in the oral pharmaceutical compositions wherein the other stabilizers include various compounds such as bisulfite, hydroquinone, 2 tert-butyl hydroquinone, and thiourea. A typical manner of making an oral pharmaceutical composition of Gallo-Torres et al. include adding an ascorbate and another stablilizer to liquid polyethylene glycol, and thereafter adding the prostaglandin active ingredient. Gallo-Torres et al., however, fail to disclose (1) an oral composition comprising a pharmaceutical active, an active solvent such as polyethylene glycol, and a reducing agent such as bisulfite, hydroquinone, 2 tert-butyl hydroquinone, and thiourea, wherein the reducing agent is solubilized in a phase of the composition other than the phase in which the active is solubilized.

Applicants submit that the Gallo-Torres et al. reference fails to anticipate Applicants' amended Claim 21 and Claims 22-36, wherein these claims are directed to oral compositions which comprise a pharmaceutical active; a hydrophilic, water-miscible, anhydrous active solvent; and a reducing agent; wherein the reducing agent is solubilized in a phase of the composition other than the phase of the composition in which the active is solubilized. Gallo-Torres et al. teach oral pharmaceutical compositions comprising a pharmaceutical active and stabilizers dissolved in a solvent such as polyethylene glycol. By contrast, Applicants' amended Claim 21 and Claims 22-36 are directed to oral (2) compositions wherein a reducing agent such as a bisulfite is solubilized in a solvent other than a hydrophilic, water-miscible, anhydrous solvent to solubilize a pharmaceutical active component.

Moreover, to anticipate Applicants' amended Claim 21 and Claims 22-36, the Gallo-Torres et al. reference should teach each and every limitation recited in these claims. Gallo-Torres et al. fail to

teach Applicants' now claimed limitation of a reducing agent being solubilized in a phase of the composition other than the phase of the composition in which the pharmaceutical active is solubilized.

In view of the foregoing remarks, Applicants submit that the Gallo-Torres et al. reference fails to teach each and every limitation of Applicants' amended Claim 21, and Claims 22-36. The rejection of these claims as being anticipated by Gallo-Torres et al. would, therefore, be improper.

Conclusions

Applicants have made an earnest effort to place the application in proper form and to distinguish the claimed invention from the prior art which had been applied in the final rejection of the parent application. WHEREFORE, entry of the preliminary amendment, consideration of the remarks made herein, and allowance of Claims 21-36 are respectfully requested.

Respectfully submitted,
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January 8, 2002
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Version with Markings to Show Changes Made

IN THE SPECIFICATION:

The specification has been amended as follows:

At page 8, lines 13-28, the paragraph has been amended as follows:

--Reducing agents are substances that have a lower redox potential than the drug or adjuvant that they are intended to protect against oxidation. Thus reducing agents are more readily oxidized than the drug or adjuvant and are effective in the presence of oxidizing agents. See W. Lund The Pharmaceutical [DODEX] CODEX, 12th Edition, p.290, The Pharmaceutical Press, 1994, incorporated herein by reference. Reducing agents of the present invention have [a] an electrode potential value. This is defined by the Nernst equation and practically measured using standard electrochemical reference cells. The resulting values are therefore called the Standard Electrode Potential, of E^0 as measured in volts of (V). Comparing standard electrode potentials for different substances can be used to assess the effectiveness of different reducing agents; see Wells, Pharmaceutical Preformulation, Ellis Horwood Limited Publishing, 1988, pp. 168-172; incorporated herein by reference. The reducing agents useful in the present invention have an Electrode Potential E^0 value greater than about -0.119V, preferably from about -0.119V to +0.250V. Preferred reducing agents are selected from the group consisting of the salts of meta bisulfite and bisulfite, including their sodium and potassium salts, dithiothreitol, thiourea, sodium thiosulphate, thioglycolic acid, [terbuty] tert-butyl hydroquinone (TBHQ), acetyl cysteine, hydroquinone, and mixtures thereof.--

IN THE ABSTRACT:

The Abstract has been amended as follows:

ABSTRACT

COMPOSITIONS HAVING IMPROVED [DELIVERY OF ACTIVES] STABILITY

The present invention pertains to liquid compositions [having] which have improved stability, and which are especially effective in the delivery of pharmaceutical actives. These compositions comprise pharmaceutical actives, solvent and a reducing agent. These compositions may take the form of liquid elixirs placed into the mouth by liquid-filled drops, metered liquid dosing devices, atomizers and liquid-releasing, edible capsules.

IN THE CLAIMS:

Claims 4-7 and 9-20 have been canceled without prejudice.

Claim 21 has been amended as follows:

Claim 21. (Amended) An oral composition comprising a pharmaceutical active in [an] a hydrophilic, water-miscible, anhydrous solvent wherein the pharmaceutical active in its un-ionized form has a percent solubility value in the solvent at ambient temperature that is equal to or greater than 0.075% and the pharmaceutical active is in [it] its free, un-ionized form as a monomolecular dispersion in the solvent, and a reducing agent wherein the reducing agent has an E^0 value equal to or greater than about -0.119V and is solubilized in a phase of the composition other than the phase of the composition in which the pharmaceutical active is solubilized.

New Claims 22-36 have been added:

--Claim 22. The composition according to claim 21 wherein the reducing agent has an E^0 value from about -0.119V to about +0.250V.--

--Claim 23. The composition according to claim 22 wherein the reducing agent is selected from the group consisting of metabisulfite salts, bisulfite salts, dithiothreitol, thiourea, sodium thiosulphate, thioglycolic acid, tert-butyl hydroquinone (TBHQ), acetyl cysteine, hydroquinone, and mixtures thereof.--

--Claim 24. The composition according to claim 23 wherein the reducing agent comprises from about 0.005% to about 1.000% by weight of the composition.--

--Claim 25. The composition according to claim 24 wherein the reducing agent comprises from about 0.1000% to about 0.01% by weight of the composition.--

--Claim 26. The composition according to claim 21 wherein the pharmaceutical active has a molecular weight of less than 500 grams per mole, is capable of being ionized when the composition comprises an aqueous solvent, and in its un-ionized form has an octanol-water partition coefficient of at least 100.--

--Claim 27. The composition according to claim 26 wherein the pharmaceutical active is selected from the group consisting of antitussives, antihistamines, non-sedating antihistamines, decongestants, expectorants, analgesic mucolytics, antipyretic anti-inflammatory agents, local anesthetics, and mixtures thereof.--

--Claim 28. The composition according to claim 27 wherein the pharmaceutical active is in the solvent at a concentration of less than or equal to 125% of the percent solubility value of said active.--

--Claim 29. The composition according to claim 28 wherein the pharmaceutical active is present in the solvent at a level from about 0.075% to about 25.0% by weight of the composition.--

--Claim 30. The composition according to claim 29 wherein the pharmaceutical active is present in the solvent at a level from about 0.28% to about 10.0% by weight of the composition--.

--Claim 31. The composition according to claim 30 wherein the solvent comprises from about 60% to about 99.975% by weight of the composition.--

--Claim 32. The composition according to claim 31 wherein the solvent comprises from about 70% to about 99% by weight of the composition.--

--Claim 33. The composition according to claim 32 wherein the solvent comprises from about 85% to about 98% by weight of the composition.--

--Claim 34. The composition according to claim 31wherein the solvent is selected from the group consisting of propylene glycol, ethanol, poly(ethylene glycol) or PEG, propylene carbonate, diethylene glycol monoethyl ether, poloxamer, glycofurol, glycerol, and mixtures thereof.--

--Claim 35. A method for treating respiratory illnesses using the composition of claim 21 wherein the method comprises oral administration of said composition having a total dosage volume of no more than 3.0 mls.--

--Claim 36. The method according to claim 35 wherein the composition is placed against any mucosal membrane of the mouth.—

ABSTRACT

COMPOSITIONS HAVING IMPROVED STABILITY

The present invention pertains to liquid compositions which have improved stability, and which are especially effective in the delivery of pharmaceutical actives. These compositions comprise pharmaceutical actives, solvent and a reducing agent. These compositions may take the form of liquid elixirs placed into the mouth by liquid-filled drops, metered liquid dosing devices, atomizers and liquid-releasing, edible capsules.